REMARKS/ARGUMENTS

After entry of this amendment, claims 14-27 are pending in the present application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 28 and 29 stand rejected for allegedly being indefinite because they are drafted as use claims. To expedite prosecution, these claims are cancelled with this amendment.

Rejections under 35 U.S.C. § 103(a)

Claim 14 stands rejected as allegedly obvious over Staveski *et al.* (US Patent No. 6,372,752) in view of Capreomycin (Drug Facts and Comparisons). Claims 15-29 stand rejected as allegedly obvious over the primary references and further in view of Montgomery (US Patent No. 6,387,886). As explained in detail below, these rejections are respectfully traversed.

The Examiner cites Staveski for teaching compounds that inhibit mycobacterial enoyl-ACP reductase and their use to treat bacterial infections both by themselves and in combination with known antibiotics, such as capreomycin. According to the Examiner, Staveski fails to teach that capreomycin inhibits *Mycobacterium tuberculosis* growth. The Examiner relies on the Capreomycin reference for this missing teaching. Staveski is also cited for allegedly teaching administration of capreomycin by inhalation.

It is well settled that the Examiner has the burden of presenting a *prima facie* case of obviousness. Analysis of obviousness under 35 U.S.C. § 103(a) requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *See, KSR Int'l Co. v. Teleflex Inc.*, 500 U.S. 398, 418 (2007), quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006). The rationale must also show that one of skill would have had a reasonable expectation of success. MPEP §2143.02.

The present rejection is improper for at least two reasons. First, the combination of the cited references fails to teach all of the elements of the claimed invention. Second, the Examiner has not properly shown that one of skill would have a reasonable expectation of success in attempting the claimed invention in view of the state of the art.

The Examiner relies on Staveski for allegedly teaching that capreomycin can be delivered by inhalation and refers to column 11, lines 39-45 of that reference. As explained below, the cited passage occurs in the context of a discussion of the delivery of the compounds ***of the invention disclosed there***, not the additional antibiotic agents such as capreomycin, as suggested by the Examiner.

The discussion of pharmaceutical formulations and routes of administration begins at column 10, line 14, where the patentees state "The compounds ***of this invention*** can be administered to a human patient by themselves or in pharmaceutical compositions..." (emphasis added). The following paragraphs then go on to discuss various routes of administration and suitable pharmaceutical composition for "the compounds." Clearly, the reference to "the compounds" in this entire section of the patent, including the language cited by the Examiner, is to the compounds of the invention. Indeed, the Capreomycin reference cited in the Office Action actually undercuts the Examiner's position in that the only routes of administration discussed there are intramuscular and intravenous administration. There is simply no basis in either of the cited references to assert that one of skill would understand the cited section of Staveski as teaching that capreomycin can be administered by inhalation.

In addition, to maintain this rejection, the Examiner must articulate reasoning and/or provide evidence to establish that one of skill would have had a reasonable expectation of success in administering capreomycin by inhalation. In view of the state of the art at the time of the invention, Applicants respectfully submit that such a showing cannot be made.

The specification provides a brief discussion of the unpredictability of administration of drugs by inhalation. (*see* paragraphs [0022] to [0025]). As explained there, due to the complexities and interactions between different types of compounds and the cells of the lung, it could not have been predicted whether inhalation administration of capreomycin could achieve therapeutic levels in the lung.

Second, it was not known whether such a local concentration in the lung would be accompanied by development of high systemic levels that would possibly result in the undesirable side effects associated with prior art systemic administration methods. As explained in paragraph [006] of the specification, although capreomycin has been used in the prior art for the treatment of pulmonary tuberculosis, it has not been a front line agent for this disease. Among the recognized problems with systemic delivery of capreomycin are renal toxicity and ototoxicity, which are a significant problem for up to 10% of patients. Indeed, such toxicity problems are highlighted in the box labeled "Warning" in the Capreomycin reference cited by the Examiner.

Surprisingly, the inventors found that therapeutically effective levels could be achieved by inhalation (*see* Figure 5A, which shows enhanced treatment of pulmonary MTB infections by aerosolized delivery compared to subcutaneous administration). In addition, the inventor's evidence indicates that local pulmonary infections can be treated without exposing the patient to potentially toxic systemic levels that occur through other routes of administration (*see*, paragraphs [0071] and [0072] and Figure 5B). Thus, the problems of renal and ototoxicities associated with the prior art can be avoided using inhalation administration.

In conclusion, the Examiner has not provided any reasoning or evidence to show that one of skill would understand that Staveski teaches that capreomycin could be administered by inhalation. If this position is maintained, the Examiner must show that one of skill would have a reasonable expectation of success in choosing this route of administration. As explained above, such a showing is not possible in view of the state of the art at the time of the invention. The evidence provided in the specification shows that the claimed methods are not only surprisingly effective in treating pulmonary MTB infections, but also avoid the toxicity problems associated with the prior art. These advantages could not have been predicted at the time of the present invention. The rejection is therefore improper and should be withdrawn.

The rejection of claims 15-29 over Staveski in view of Capreomycin and further in view of Montgomery is respectfully traversed. Staveski and Carpreomycin are cited for the same teachings noted above. Montgomery is relied on for teaching various claim limitations in claims 15-29. As explained above, neither of the primary references disclose or suggest that

capreomycin can be administered by inhalation. Nothing in the Office Action shows how Montgomery addresses these defects. In the absence of such a showing the rejection of claims 15-29 is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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